Afatinib as first-line treatment in patients with *EGFR*-mutated non-small cell lung cancer in routine clinical practice

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Supplemental material A: *EGFR* mutation analysis

EGFR mutation analysis was most often performed on primary tumour tissue (80.3%), or metastatic tumour tissue (13.8%). The techniques most frequently used for analysis were PCR (34.9%) and Sanger sequencing (29%), and results were most often available within 7 days (36.8%). Analysis of exon 18 and exon 20 was performed only in 7.9% and 2.0% of patients, respectively, whereas exon 19 and exon 21 were analysed in 67.1% and 25.7% of patients, respectively. Testing for exon 20 insertions was not mandatory and was dependent on the pathological institute analysing the biopsy.

Supplemental Table S1. *EGFR* mutation analysis.

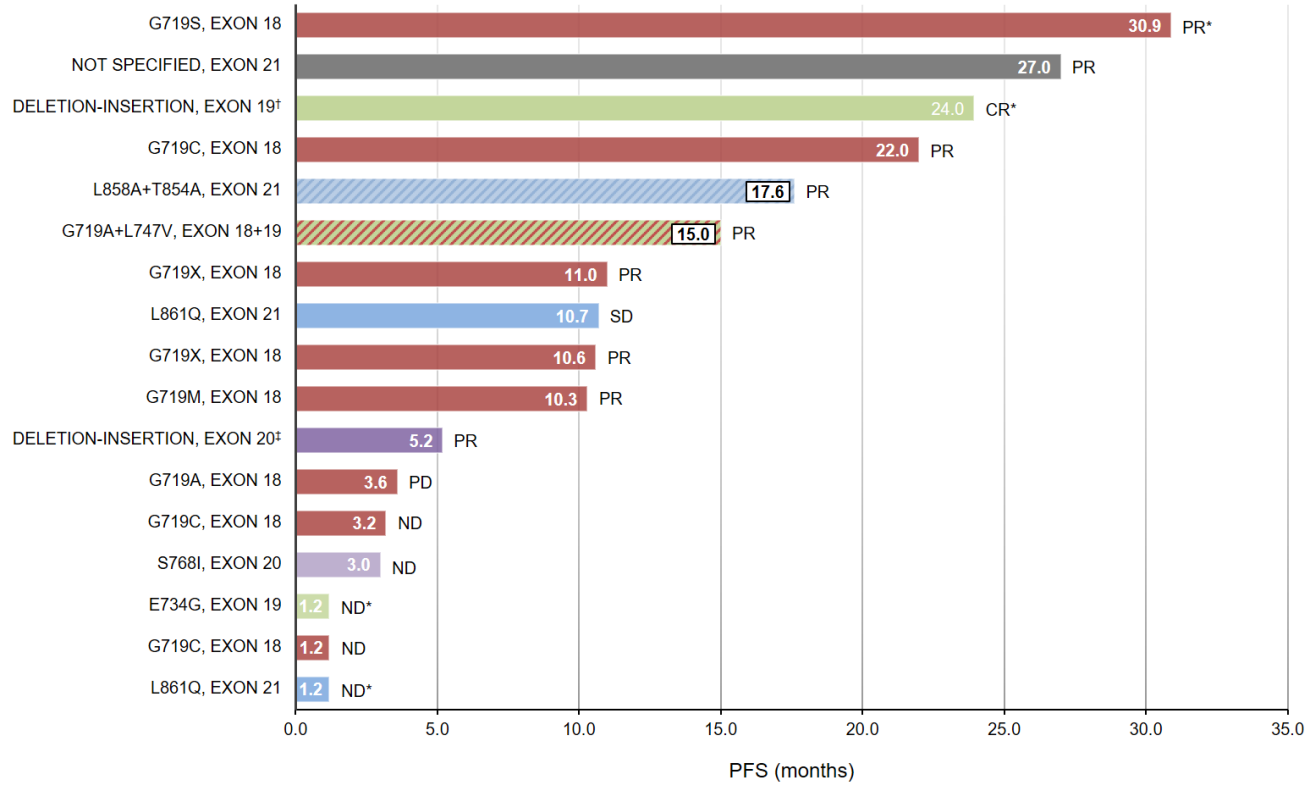
***EGFR* mutation analysis**	**Total**
Number of patients, *N* (%)	152 (100)
Localisation of tumour tissue*, *n* (%)	
Primary tumour	122 (80.3)
Metastasis	21 (13.8)
Lymph nodes	7 (4.6)
Not specified	4 (2.6)
Detection method*, *n* (%)	
Polymerase chain reaction	53 (34.9)
Sanger sequencing	44 (30.0)
Next-generation sequencing	25 (16.5)
Pyrosequencing	4 (2.6)
Fragment length analyses	3 (2.0)
Other method	6 (4.0)
Not specified	31 (20.4)

*Multiple answers are possible.
EGFR, epidermal growth factor receptor.

Supplemental Figure S1. PFS of patients in the PPS with uncommon *EGFR* mutations.

*No PFS event at time of data cut-off; †Exon 19 deletion-insertion: c.2240_2260delinsCCG, p.Leu747_Lys754delinsSerGlu; ‡Exon 20 deletion-insertion: N771delinsGY, c.2311delinsGGTT. The following uncommon mutations (and best responses, if known) were observed in patients who were not part of the PPS (*n*=3 patients): G719X in exon 18 (SD); c.G2084T, p.S695I in exon 18 (ND); an unspecified point mutation in exon 19 (PD).

Abbreviations: CR, complete response; ND, not reported; PPS, per protocol set; PR, partial response; SD, stable disease.



Supplemental material B: EORTC QLQ-C30/LC13 – Change between start and end of therapy

EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires were used to monitor the changes in QoL and tumour-related symptoms. Scores for each scale and single-item measure were transformed linearly to a score ranging from 0 to 100. Improvement and worsening were defined as a change in score of ≥10 points from baseline. Questionnaires were completed by 35 patients at the start and end of treatment.

Supplemental Table S2. Time to worsening of symptoms, indicated by a ≥10-point increase from baseline of QLQ-C30/LC13 scores by Kaplan–Meier analysis.

Symptom	Patients, *n*	Worsening, *n* (%)	Censored, *n* (%)	Median, months (95% CI)
Coughing	119	35 (29.4)	84 (70.6)	33.9 (17.9–NR)
Dyspnoea	118	44 (37.3)	74 (62.7)	22.2 (13.7–NR)
Pain	119	53 (44.5)	66 (55.5)	18.3 (9.2–23.7)

NR, not reached.

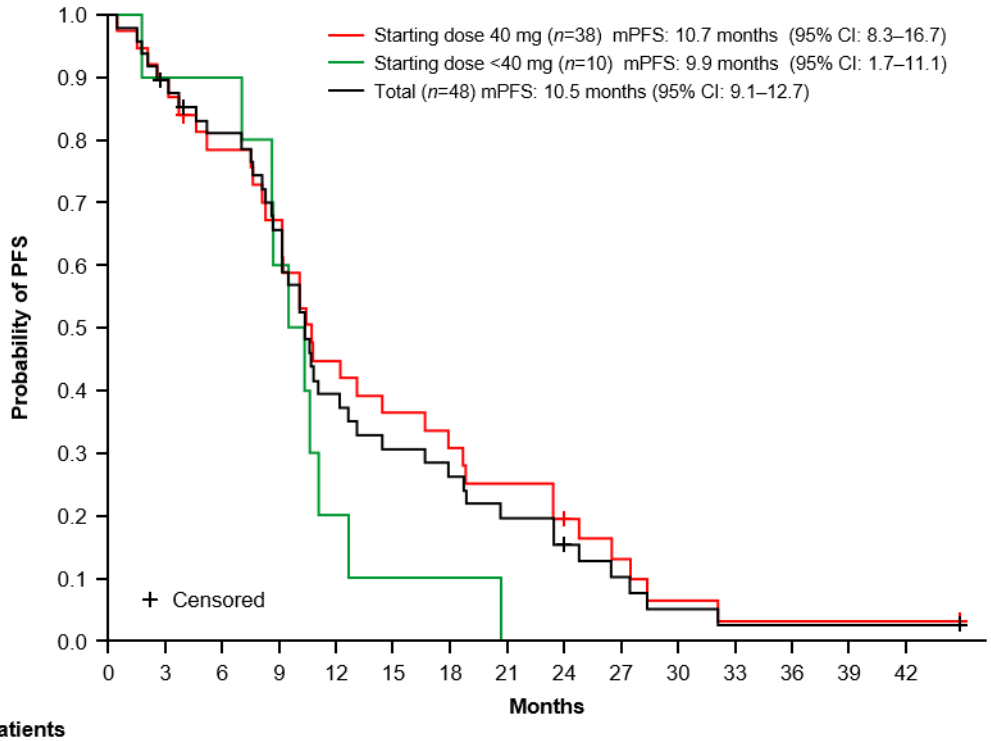
Supplemental Table S3. EORTC QLQ-C30/LC13 outcomes.

Patients (*n*=35)	Improved, *n* (%)	Stable, *n* (%)	Worsened, *n* (%)	Missing, *n* (%)
Coughing	15 (42.9)	15 (42.9)	4 (11.4)	1 (2.9)
Dyspnoea	19 (54.3)	4 (11.4)	12 (34.3)	–
Short of breath	6 (17.1)	23 (65.7)	6 (17.1)	–
Pain	11 (31.4)	11 (31.4)	13 (37.1)	–
Pain in chest	6 (17.1)	20 (57.1)	9 (25.7)	–
Pain in arms/shoulder	10 (28.6)	13 (37.1)	12 (34.3)	–
Pain in other parts	9 (25.7)	10 (28.6)	16 (45.7)	–
QoL/Global health status	16 (45.7)	9 (25.7)	10 (28.6)	–

QoL, quality of life.

Supplemental material C. Progression-free survival (PFS, months) in patients with brain metastases by starting dose

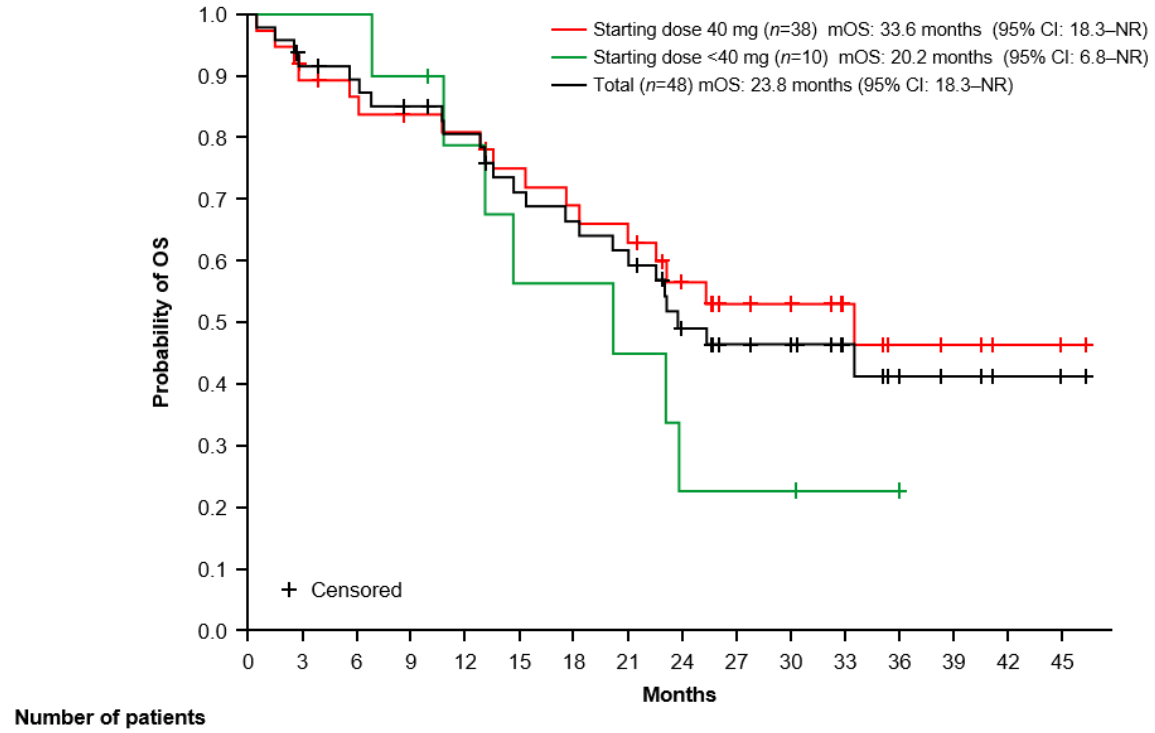
Supplemental Figure S2. PFS (months) in patients with brain metastases by starting dose. Abbreviations: CI, confidence interval; mPFS, median progression-free survival: PFS, progression free survival.



Number of patients															
Starting dose 40 mg	38	33	28	24	16	13	11	9	6	4	2	1	1	1	1
Starting dose <40 mg	10	9	9	6	2	1	1	0	0	0	0	0	0	0	0
Total	48	42	37	30	18	14	12	9	6	4	2	1	1	1	1

Supplemental material D. Overall survival (OS, months) in patients with brain metastases by starting dose

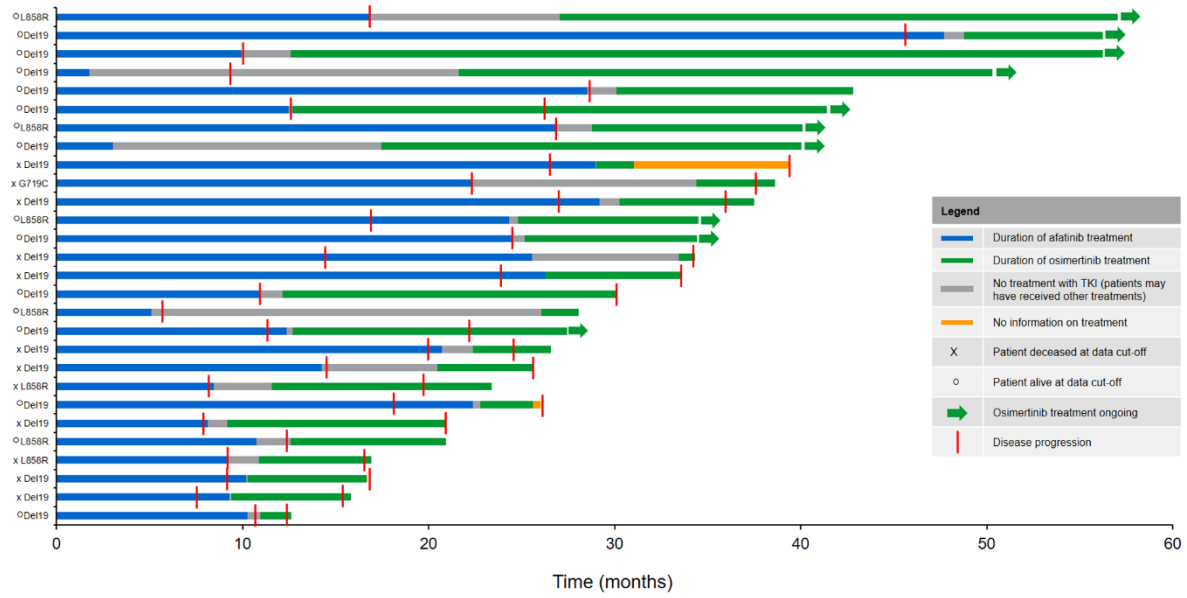
Supplemental Figure S3. OS (months) in patients with brain metastases by starting dose. Abbreviations: CI, confidence interval; mOS, median overall survival; NR, not reached; OS, overall survival.



Number of patients																
Starting dose 40 mg	38	33	31	29	28	25	23	22	16	12	10	8	5	4	2	1
Starting dose <40 mg	10	10	10	9	7	5	5	4	2	2	2	1	0	0	0	0
Total	48	43	41	38	35	30	28	26	18	14	12	9	5	4	2	1

Supplemental Material E. Outcomes in patients who received osimertinib following afatinib

Supplemental Figure S4. Outcomes in patients who received osimertinib following afatinib (*n*=28). Abbreviation: TKI, tyrosine kinase inhibitor.



Supplemental material F. Characteristics, PFS and OS of patients in LUX-Lung 3, LUX-Lung 6, LUX-Lung 7, and GIDEON

Supplemental Table S4. Characteristics, PFS and OS of afatinib-treated patients in LUX Lung 3, LUX Lung 6, LUX-Lung 7, and GIDEON.

	LUX-Lung 3 (*n*=230)[1,2]	LUX-Lung 6 (*n*=242)[2,3]	LUX-Lung 7 (*n*=160)[4,5]	GIDEON (*n*=152)
Sex, *n* (%)				
Male	83 (36)	87 (36)	69 (43)	46 (30)
Female	147 (64)	155 (64)	91 (57)	106 (70)
Median age, years (range)	62 (28–86)	58 (29–79)	63 (30–86)	67 (38–89)
Ethnicity, *n* (%)				
Asian	166 (72)	242 (100)	94 (59)	Not collected
Non-asian	64 (28)		66 (41)	Not collected
Histology, *n* (%)				
Adenocarcinoma	230 (100)	242 (100)	159 (99)	139 (91)
Other	0	0	1 (1)*	13 (9)†
Stage, *n* (%)				
IIIB	20 (9)‡	16 (7)§	8 (5)	0
IV	210 (91)	226 (93)	152 (95)	150 (99)
Other	0	0	0	2 (1)
Baseline ECOG status, *n* (%)				
0	92 (40)	48 (20)	51 (32)	73 (48)
1	138 (60)	194 (80)	109 (68)	65 (43)
2	0	0	0	4 (3)
3	0	0	0	3 (2)

Not assessed	0	0	0	7 (5)
***EGFR* mutation, *n* (%)**				
Exon 19 deletion	112 (49)	124 (51)	93 (58)	98 (64)
Leu858Arg	91 (40)	92 (38)	67 (42)	34 (22)
Uncommon mutations	27 (12)	26 (11)	0	20 (13)
Smoking status, *n* (%)				
Never	155 (67)	181 (75)	106 (66)	64 (42)
Former	70 (30)	44 (18)	21 (13)[¶]	47 (31)
Current	5 (2)	17 (7)	33 (21)**	10 (7)
Not specified	0	0	0	31 (20)
Median PFS, years (95% CI)	11.1 (not reported)	11.0 (9.7–13.7)	11.0 (10.6–12.9)	12.2 (10.5–16.0)
Median OS, years (95% CI)	28.2 (24.6–33.6)	23.1 (20.4–27.3)	27.9 (not reported)	30.4 (23.6–39.0)

[*]Mixed histology (dominant histology: adenocarcinoma). [†]Mixed (NSCLC/SCLC) (*n*=5, 3%); squamous cell carcinoma, large cell carcinoma, mixed (adeno-squamous) (*n*=1, 1% each); not determined (*n*=5, 3%). [‡]IIIb with pleural effusion. [§]IIIb with pleural effusion or pericardial effusion. [¶]Light ex-smokers (<15 pack-years and stopped more than 1 year before diagnosis). **Current smokers or-ex smokers with other smoking histories.
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer.

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